Organic Acidemias Part II PA, IVA, 3-MCCD, and Biotin-Related Disorders

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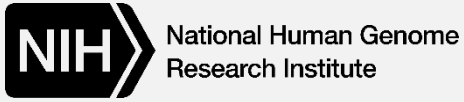
Oleg Shchelochkov, MD

Senior Clinician
Associate Investigator
Director of Residencies and Fellowship Programs
NHGRI, NIH
Bethesda, Maryland, USA

Charles P. Venditti, MD, PhD

Senior Investigator
Head, Organic Acid Research Section (OAR)
NHGRI, NIH



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Disclosures

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Where do we live and practice?

Please name the country of your clinical or laboratory practice in the chat

CME GOALS

- Overview selected organic acidemias (PA, IVA, 3-MCCD, and biotin-related IEMs)
  - HETEROGENEOUS
- Review clinical manifestations and disease mechanisms
  - MULTIORGAN PATHOLOGY, DIVERSE SYMPTOMS AND SIGNS
- Discuss treatment approaches
  - MEDICAL, SURGICAL, AND EXPERIMENTAL

A Newborn with Lethargy

A 2 day-old newborn girl became lethargic in the last 24 hrs. Her electrolytes are Na 135, K 5, Cl 100, HCO_3 10. Her glucose is 71. Her ammonia level is 120 umol/L. You receive a phone call about an abnormal newborn screen on this patient. Which abnormality is most likely being reported?

A. Elevated C3 (PA or MMA)

B. Abnormal phenylalanine (PKU)

C. Elevated 17-hydroxyprogesteron (CAH)

D. High TSH (1^o congenital hypothyroidism)

E. Elevated citrulline (classic citrullinemia)

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- "HAGMA"
  - Lactate
  - Ketone bodies
  - Methylmalonate
  - Pyroglutamate
- Ammonia level

Question 2

A 3-year-old patient with the known diagnosis of biotinidase deficiency presents with speech delay, lack of social reciprocity, and stereotypical behaviors. Non-compliance with biotin supplementation is denied. Physical exam is unremarkable. What is the BEST next step?

A. Refer for additional genetic evaluation

B. Obtain urinary organic acids

C. Order *BTD* gene analysis

D. Increase biotin from 5 to 10 mg/day

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- A departure from the typical clinical course
- Lack of physical findings argues against chronic non-compliance

Jay AM et al, GiM, 2014
https://www.sciencedirect.com/science/article/pii/S1098360021028446?via%3Dihub

An Isolated Elevation of C5-OH

You received a call from the newborn screen program about an isolated elevation of C5-OH. What is the most likely diagnosis?

A. Biotinidase deficiency

B. 3MCC deficiency

C. 3-Methylglutaconic acidemia type 1

D. HMG-CoA lyase deficiency

E. Holocarboxylase synthetase deficiency

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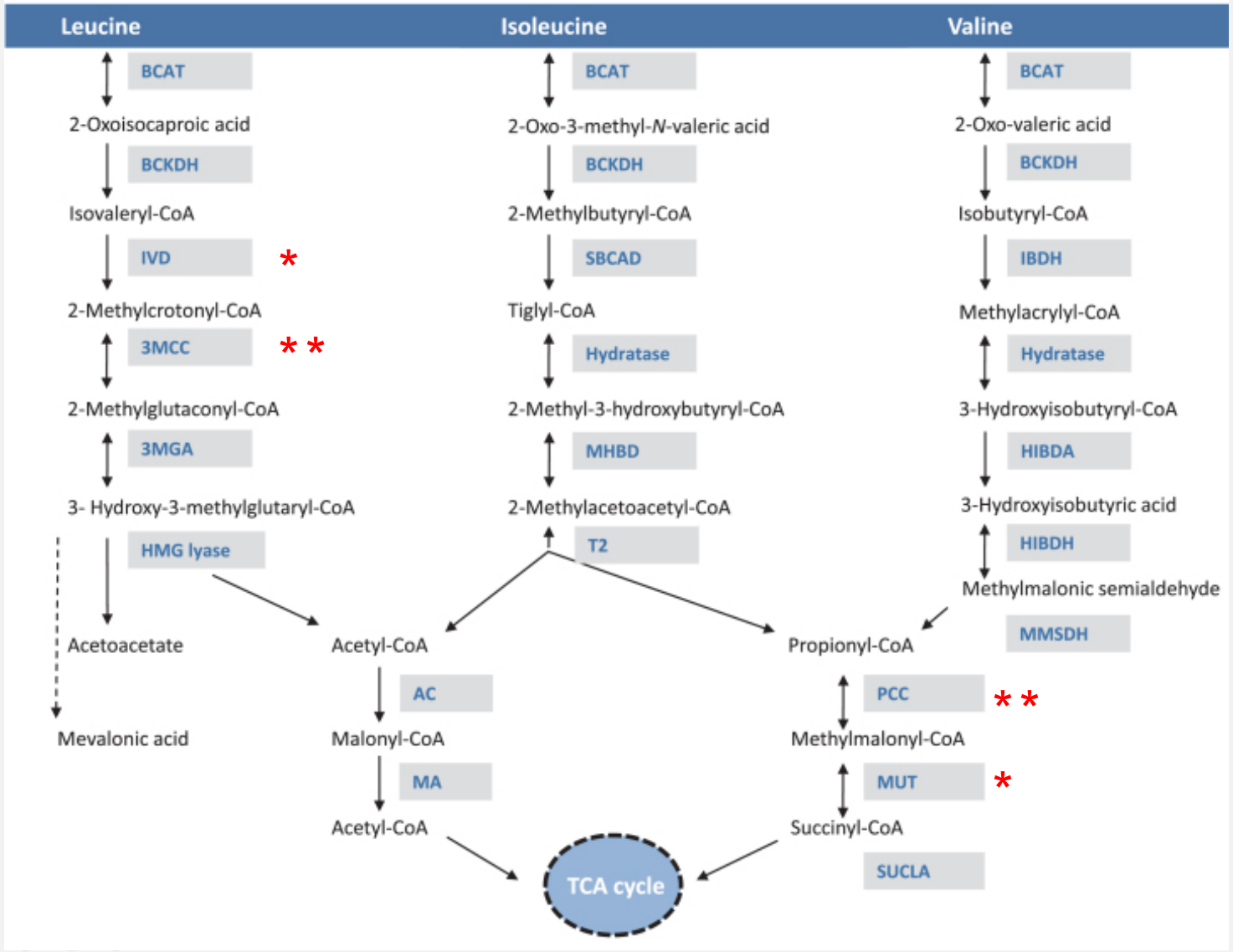
E. Holocarboxylase synthetase deficiency

- Isolated elevation of C5-OH
- Disease prevalence

ORGANIC ACIDEMIA/ACIDURIA

- IEMs characterized by the excretion of non-amino, carbon-based acids in the body fluids
- Majority are caused by defects in the oxidation of branched-chain amino acids or lysine
  - Examples: MMA, PA, IVA, GA 1, BKT, [MSUD]
- Incidence: As a group may be as common as 1:5-20,000
- Clinical manifestations: DIVERSE and SEVERE
- Outcomes: vary by disease, generally prognosis is guarded; cognitive impairment common but NOT uniform



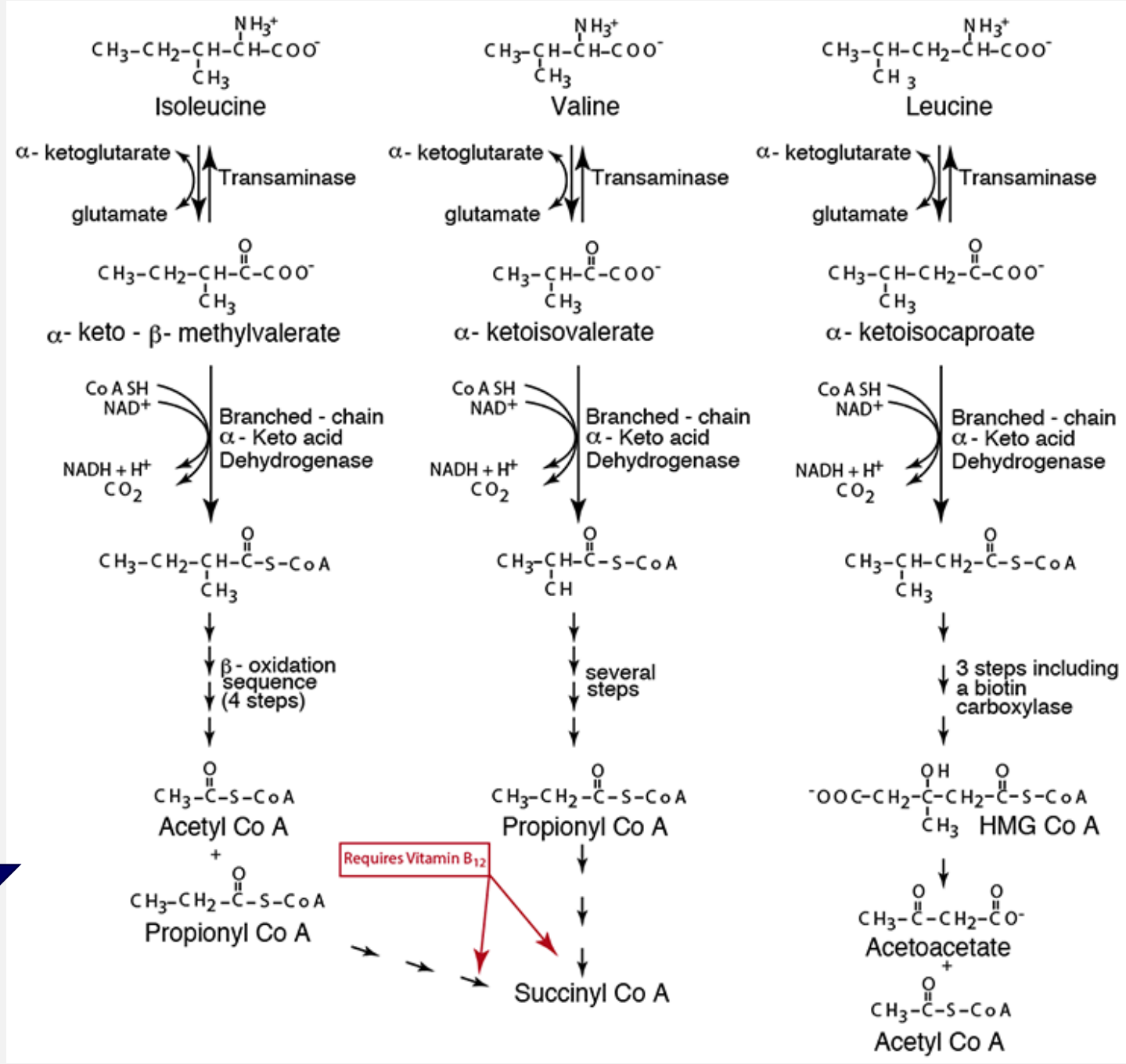
Manoli I, Venditti CP. Disorders of branched chain amino acid metabolism. Transl Sci Rare Dis. 2016 7;1(2):91-110. PMCID: PMC5685199.

Ile, Val, Leu
ESSENTIAL AMINO ACIDS

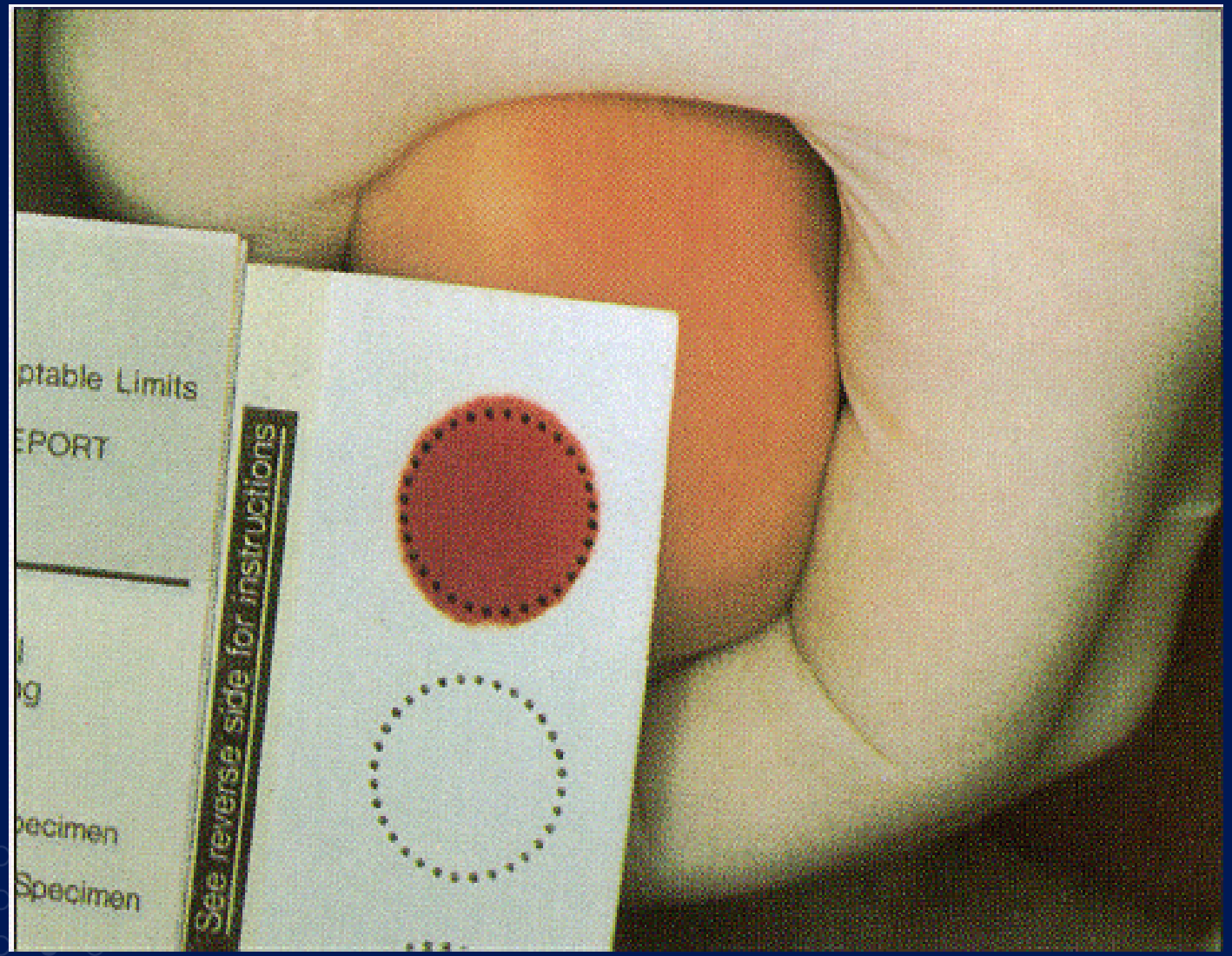
REVERSIBLE (BCAT)
TRANSAMINATION

IRREVERSIBLE (BCKDH)
OXIDATIVE
DECARBOXYLATION

ORGANIC ACIDEMIAS
OBLIGATE METABOLISM
CARBON LOSS
ENERGY PRODUCTION



Universal Newborn Screening


ptable Limits
EPORT
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pecimen
Specimen
See reverse side for instructions

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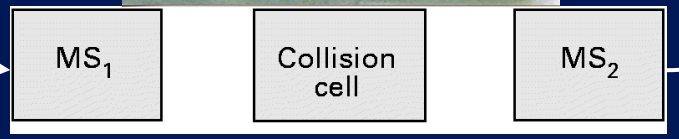
Newborn Screening Using LC MSMS ~ 1999

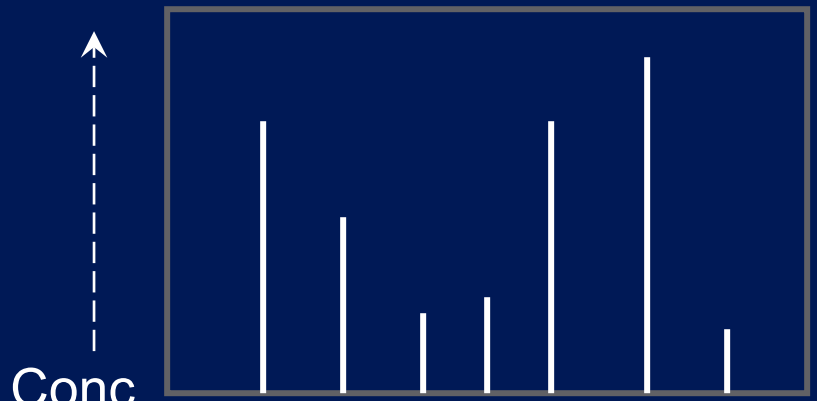
Drop of blood from infant's heel

Filter paper

Sample preparation (automated)



SPECTRUM



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Newborn Screening in USA circa 2021

CORE

9 OA (MUT, CblA, B, PROP, IVA, GA I, HMG, MCD, BKT, 3-MCC)
5 FAO (MCAD, VLCAD, LCHAD, TFP, CUD)
6 AA (PKU, MSUD, HCY, CIT, ASA, TYR I)

SECONDARY TARGETS

9 OA (CblC,[D,F,J,TcblR,X]; MAL, IBG, 2M3HBA, 2MBG, 3MGA)
8 FAO (SCAD, GA2, M/SCHAD,MCKAT, CPT II, CACT, CPT IA, DERED)
8 AA (HYPERPHE, TYR II, BIOPT, ARG, TYR III, MET, CIT II)

Emerging: LSDs (MPS1, Pompe, Gaucher, Fabry), SCIDs, Krabbe (NY), peroxisomal disorders … + HTS

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Biochemical Findings in Common Inborn Errors of Metabolism

MARZIA PASQUALI,* GAVIN MONSEN, LEAH RICHARDSON, MARTHA ALSTON, AND NICOLA LONGO

The application of tandem mass spectrometry (MS/MS) to newborn screening has led to the detection of patients with a wider spectrum of inborn errors of metabolism. A definitive diagnosis can often be established early enough to start treatment before symptoms appear. Here, we review common biochemical findings in disorders caused by deficiency of 3-methylcrotonyl-CoA carboxylase, isobutyryl-CoA dehydrogenase, 2-methyl-3-hydroxybutyryl-CoA dehydrogenase, 3-ketothiolase, 2-methylbutyryl-CoA dehydrogenase, and medium chain acyl CoA dehydrogenase. The diagnosis of these disorders requires biochemical confirmation by measurement of plasma acylcarnitine profile, urine organic acids, and urine acylglycine profiles followed by measurement of enzyme activity or detection of causative mutations. Early treatment can improve the outcome of these disorders.

KEY WORDS: newborn screening; tandem mass spectrometry; organic acidemias; urine acylglycine; urine acylcarnitine

How to cite this article: Pasquali M, Monsen G, Richardson L, Alston M, Longo N. 2006. Biochemical findings in common inborn errors of metabolism. Am J Med Genet Part C Semin Med Genet 142C:64–76.

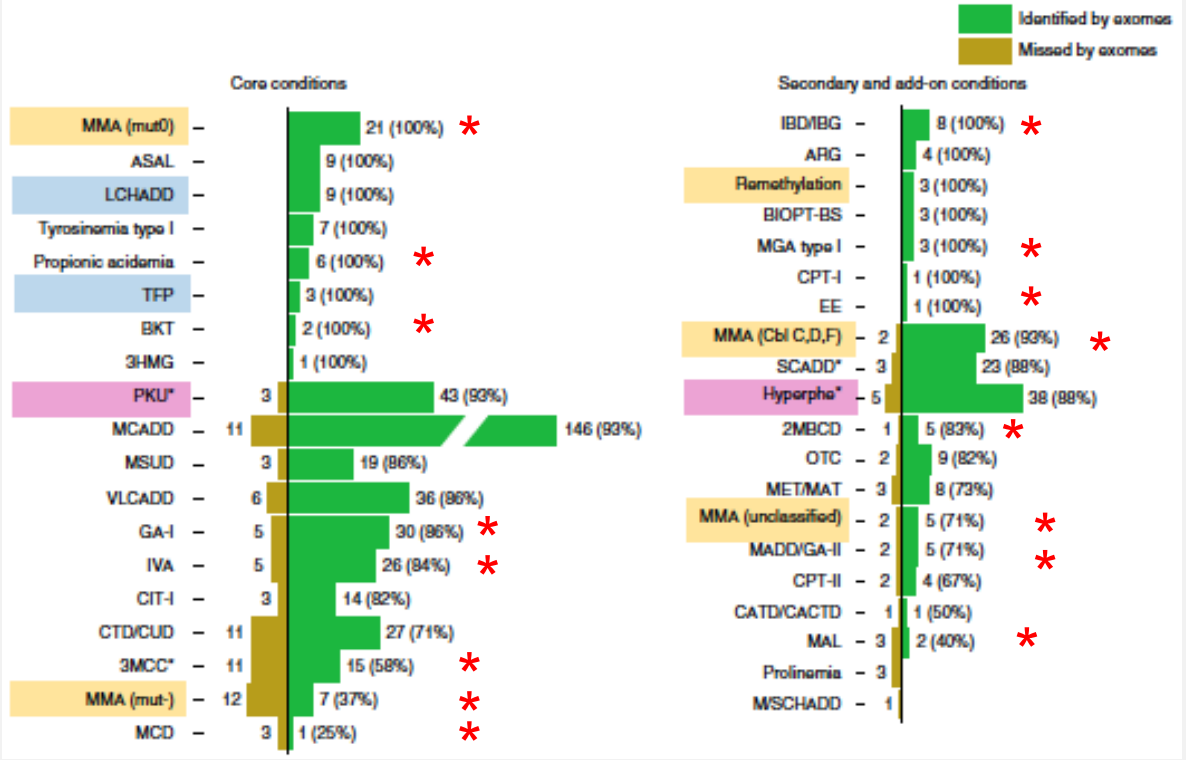
TABLE II. Organic Acidemias Identifiable by Newborn Screening

Abnormal acylcarnitine	Possible causes	Additional tests	Signs/symptoms	Therapy
High C3	Propionic acidemia Methylmalonic acidemia Prematurity Diet low in vitamin B12	Plasma ammonia, basic metabolic panel, plasma amino acids, plasma acylcarnitine profile, urine organic acids, serum biotinidase	Metabolic acidosis, hyperammonemia, coma, hypotonia or hypertonia	Special diet, carnitine, vitamin B12, biotin, other vitamins
High C5	Isovaleric acidemia (leucine metabolism) 2-methylbutyryl-CoA dehydrogenase deficiency (isoleucine metabolism) Medications (antibiotics)	Plasma ammonia, basic metabolic panel, plasma amino acids, plasma acylcarnitine profile, urine organic acids and acylglycine profile	Metabolic acidosis, hyperammonemia, coma	Special diet, carnitine, glycine
High C4	Isobutyryl CoA dehydrogenase deficiency (valine metabolism) SCAD deficiency	Plasma acylcarnitine profile, plasma amino acids, urine organic acids, acylglycine and acylcarnitine profile	Failure to thrive, carnitine deficiency, cardiomyopathy	Carnitine
High C5-DC	Glutaric acidemia type 1 Kidney disease	Plasma acylcarnitine profile, urine organic acids and acylcarnitine profile	Macrocephaly, brain atrophy, hypotonia, dystonia, degeneration of basal ganglia	Special diet, carnitine, vigorous treatment of fever and infections
High C5-OH	3-Methylcrotonyl CoA carboxylase (MCC) deficiency (leucine metabolism) Maternal MCC deficiency Biotinidase deficiency Prematurity	Plasma acylcarnitine profile, urine organic acids and acylglycine profile, serum biotinidase activity	Developmental delays, metabolic acidosis, hypoglycemia	Carnitine, low-protein diet
High C5-OH, C5:1	3-Ketothiolase deficiency (isoleucine metabolism) 2-methyl-3-hydroxybutyryl-CoA dehydrogenase deficiency	Plasma ammonia, basic metabolic panel, plasma amino acids, plasma acylcarnitine profile, urine organic acids	Metabolic acidosis, vomiting, headaches, occasional hyperammonemia	Low-protein diet, fasting avoidance, carnitine
High C6-DC, C5-OH	3-OH 3-CH3 glutaryl CoA Lyase deficiency Prematurity Ketosis	Comprehensive metabolic panel, plasma ammonia, plasma amino acids, plasma acylcarnitine profile, urine organic acids	Hypoglycemia, mental retardation, epilepsy	Fasting avoidance, carnitine, IV glucose, vigorous treatment of infections
High C5:1, C3, C5-OH	Holocarboxylase synthase deficiency Biotinidase deficiency	Comprehensive metabolic panel, plasma ammonia, plasma amino acids, plasma acylcarnitine profile, urine organic acids, serum biotinidase, fibroblast studies	Vomiting, ketoacidosis, dehydration, coma, skin rash, alopecia	Biotin

LETTERS
https://doi.org/10.1038/s41591-020-0966-5
nature medicine

The role of exome sequencing in newborn screening for inborn errors of metabolism

Aashish N. Adhikari[1,2] ✉, Renata C. Gallagher[2,3], Yaqiong Wang[1], Robert J. Currier[3], George Amatuni[3], Laia Bassaganyas[2], Flavia Chen[2,4], Kunal Kundu[1,5], Mark Kvale[2], Sean D. Mooney[6], Robert L. Nussbaum[2,7], Savanna S. Randi[8], Jeremy Sanford[8], Joseph T. Shieh[2,3], Rajgopal Srinivasan[5], Uma Sunderam[5], Hao Tang[9], Dedeepya Vaka[2], Yangyun Zou[1], Barbara A. Koenig[2,4], Pui-Yan Kwok[2,10,11], Neil Risch[2,12], Jennifer M. Puck[2,3,10,13,16] ✉ and Steven E. Brenner[1,2,14,15,16] ✉



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Organic Acidemias Are Multisystemic Disorders

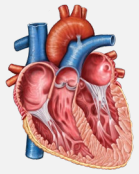
Hyperammonemia
metabolic acidosis

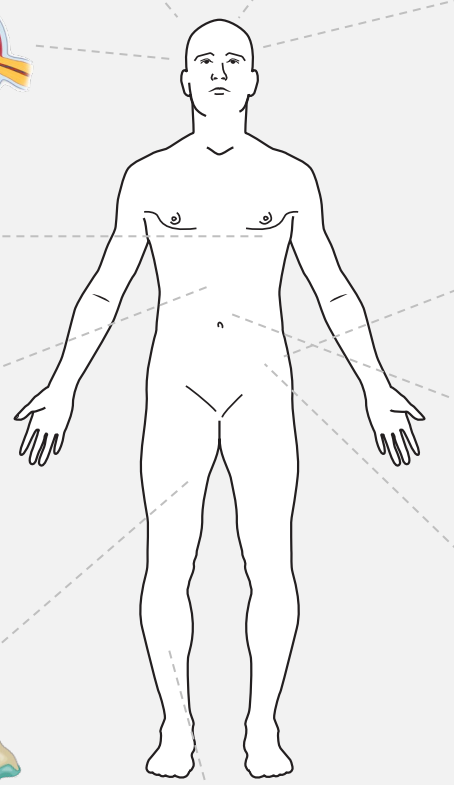
Intellectual impairment
Basal ganglia stroke
Hyperammonemia

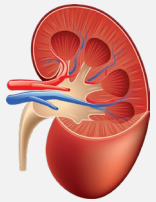
Optic nerve atrophy

Sensorineural hearing loss

Long QT interval
Arrhythmias
Cardiomyopathy

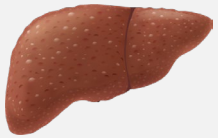




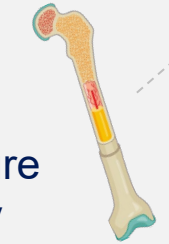


Chronic renal failure

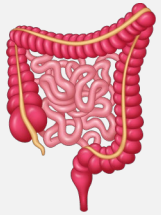
Hepatomegaly
Fatty liver



Pancreatitis



Osteopenia
Bone marrow failure
Immunodeficiency



GI dysmotility, G/J tube
dependence

Dermatitis

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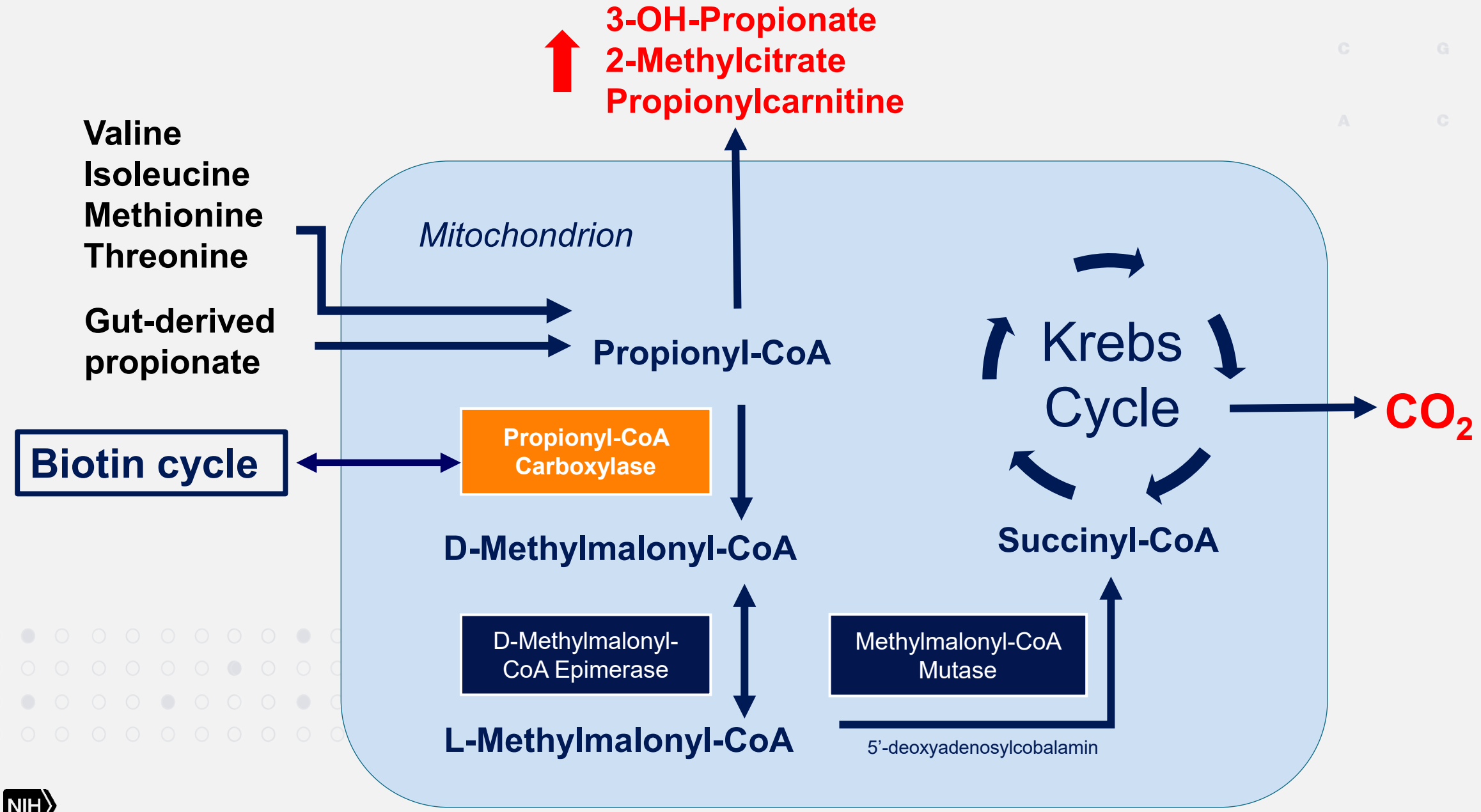
Propionic Acidemia


3-OH-Propionate
2-Methylcitrate
Propionylcarnitine
Valine
Isoleucine
Methionine
Threonine
Gut-derived propionate
Biotin cycle
Mitochondrion
Propionyl-CoA
Propionyl-CoA Carboxylase
D-Methylmalonyl-CoA
D-Methylmalonyl-CoA Epimerase
L-Methylmalonyl-CoA
Methylmalonyl-CoA Mutase
5'-deoxyadenosylcobalamin
Krebs Cycle
Succinyl-CoA
CO_2

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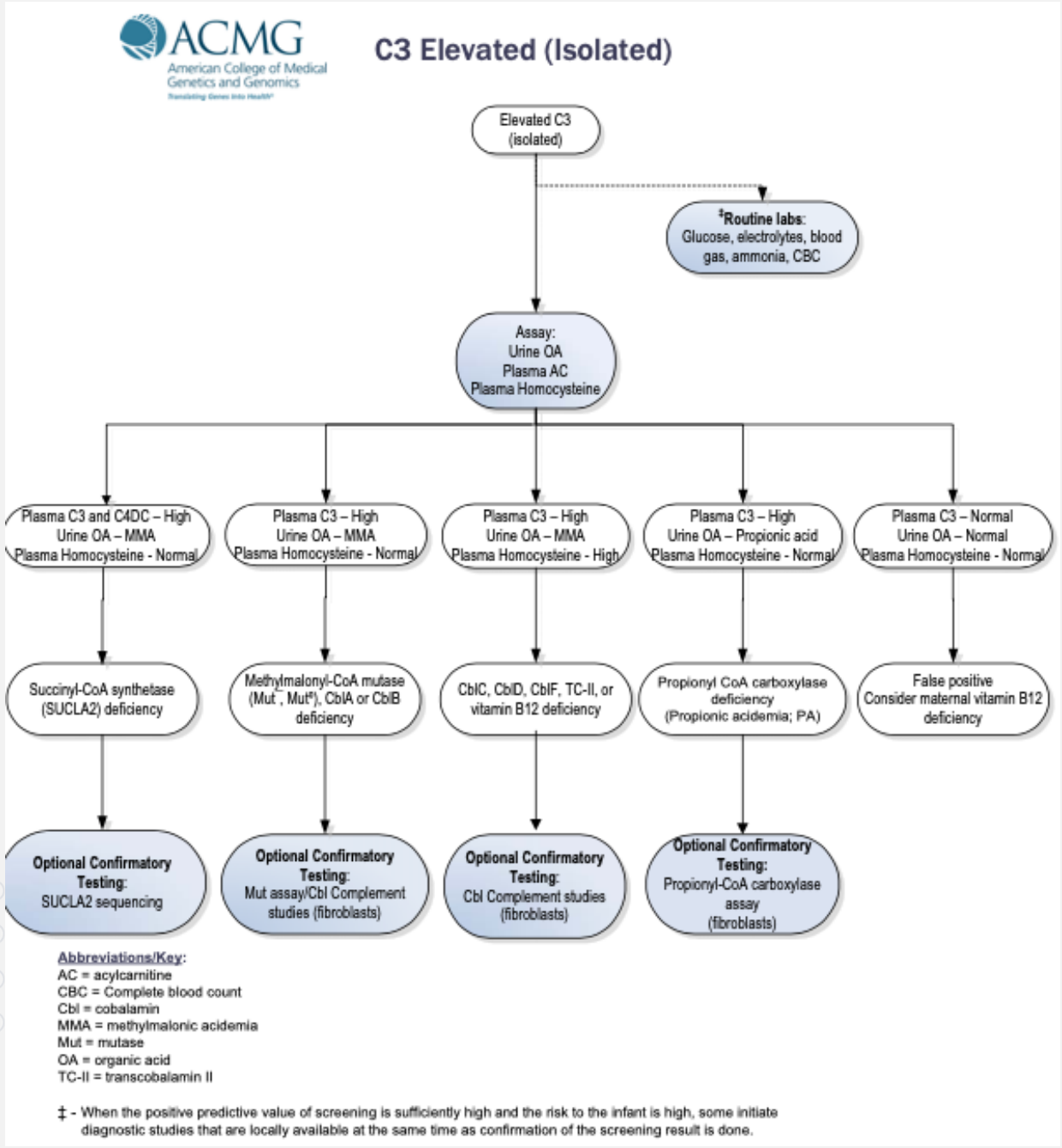

Comments:

- for PA, the UOA shows massive 2-MC and no MMA
- Testing is usually molecular vs enzymatic

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MS/MS of Acylcarnitines in Blood Spots

- Primary markers: Elevated C3
- Secondary markers: C3/C2, C3/C16
- C3 AND C3/C2 vs C3 OR C3/C2
- Second-tier testing: urine organic acid assay, plasma acylcarnitine profile, total and free carnitines, plasma amino acids (glycine, methionine, glutamine), total plasma homocysteine
- Molecular confirmation: PCCA and PCCB (panels)

Metabolic Studies: PA

- Plasma acylcarnitine profile: elevated C3
- Urine organic acids:
  - Presence of
    - 3-hydroxypropionate
    - 2-methylcitrate
    - tiglylglycine
    - propionylglycine
    - lactic acid
  - Absence of methylmalonic acid
- Plasma amino acids: elevated glycine, low glutamine, normal methionine
- Normal total plasma homocysteine

NBS Pitfalls

- An infant with “mild” forms of PA (e.g. Amish genotype)
  - May not be identified by the NBS in the US and may have an unrevealing UOA
- MethylmalonicS acidemia
- Maternal B_{12} deficiency
- Multiple carboxylase deficiency (holocarboxylase synthetase or biotinidase)
- Carbonic anhydrase VA deficiency (abnormal UOAs with normal ACP)
- Mitochondrial disorders

DIAGNOSIS OF PA - CLINICAL SYNDROMES

- Neonatal crisis (common)
  - Hyperammonemia, with severe metabolic acidosis, ketonuria
- Failure to thrive with hypotonia (common)
- Vomiting and GI distress (common)
  - Mimics feeding intolerance
  - Late onset/partial deficiency
- Acute encephalopathy with AG metabolic acidosis
  - Can mimic methanol/PEG intoxication, r/o DKA
- Immunodeficiency and cytopenias
- Reye-like syndrome
- Movement disorder (dystonia)
- Cardiomyopathy/sudden death

A Sick Newborn with Pending NBS

- High-anion gap metabolic acidosis
- Hyperammonemia
- Lactic acidosis
- Elevated plasma and urinary ketones
- Low to normal blood glucose
- Neutropenia, anemia, and thrombocytopenia

Management at the Hospital

Trigger causing catabolism (intercurrent illness, fever, prolonged fasting)

↓

(Imminent) acute metabolic decompensation

- Stop protein intake (for 24-48 hours maximum)
- Start glucose IV at age-appropriate rate (avoid hyperglycaemia by using insulin, supplement sodium and potassium)
- Double carnitine dose to 200 mg/kg/day, give IV if orally not tolerated
- Monitor acid-base balance, ammonia and electrolyte levels

↓

Raised ammonia levels

- **100-250 µmol/L**: Start sodium benzoate (250 mg/kg bolus over 90 minutes, then 250 mg/kg over 24 hours), consider carglumic acid (100 mg/kg bolus, then 50 mg/kg bolus every 6 hours)
- **250-500 µmol/L**: Same as above; prepare for extracorporeal detoxification and start if significant encephalopathy is present or ammonia control is difficult with above drug regimen
- **>500 µmol/L**: Same as above and start with extracorporeal detoxification

Forny et al, JIMD, 2021

Management at Home

- At-home detection and monitoring of urine ketones is likely not useful
- Diet modification under the direction of the metabolic team – practice specific
- If fever is present due to a mild infection, treatment may include paracetamol and ibuprofen (beware of CKD!)

Controversial Topics

- Suppression of anaerobic gut microflora
  - Oral metronidazole
  - Oral rifaximin
- Probiotics
- Biotin supplementation
  - TSH, T3, T4
  - PTH
- Levocarnitine
  - Ranges 50 – 200 mg/kg/day
  - 100 mg/kg/day is likely optimal
  - Plasma free carnitine
- Long QTc intervals (e.g. ondansetron or loperamide)
- Valproic acid
- Central line access

Dietary Management

- Low protein diet without medical foods?
- Use of medical foods?
  - Incomplete protein – ratio?
  - Carb/fat mixes (DuoCal vs Pro-Phree)
- G-tube
- Overnight feedings
- Sick day diets

Monitoring in Young PA Patients

- Risk stratification
  - Plasma C3
  - Plasma 2MC
  - GDF15
  - Genotype
- Routine labs – until a trend is established
  - Plasma amino acids (2 hours after the last feed) – while adjusting diet
  - CBC
  - 25-OH Vitamin D
  - TSH with reflex FT4
  - TG
  - Pro-BNP
- Growth
  - Pediatric schedule
- Skin – rashes?
- Screening for autism spectrum disorder
- Seizures and movement disorder
- Eye exam and hearing evaluation
- Abdominal US
- ECHO, EKG, Holter

Monitoring of PA: Unresolved questions

- Alpha-fetoprotein
  - Reserve for patients with elevated ALT/AST in the 3rd decade of life?
- Creatinine-based vs Cystatin C-based eGFR
- Optimal age to start ECHO, EKG and Holter

Transplantation in PA

Indications (Liver, Liver-Kidney, Kindey, Heart)

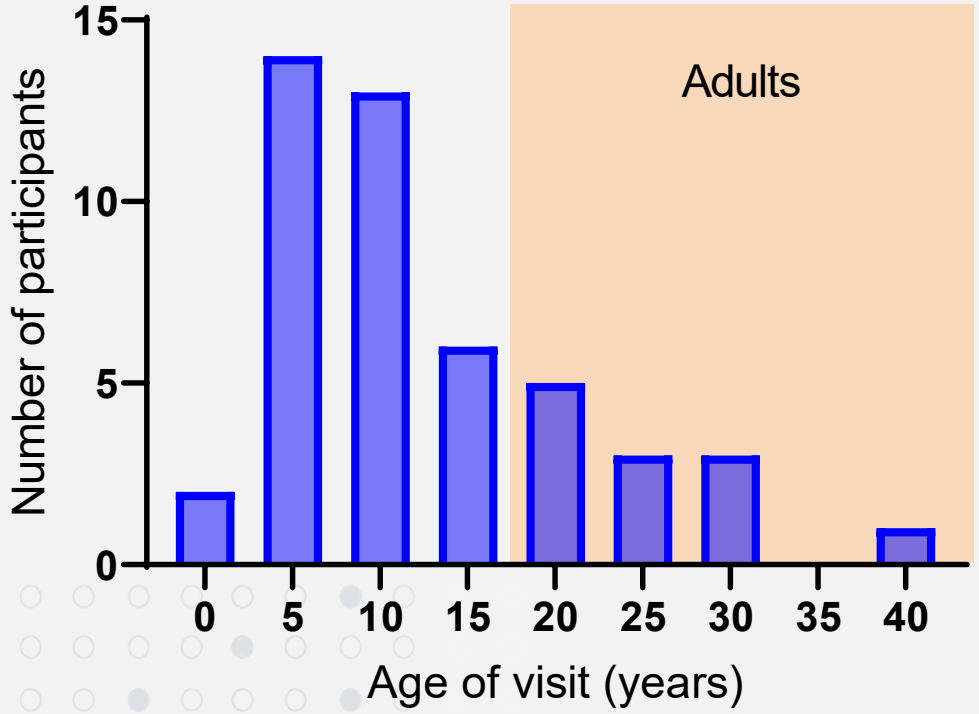
- Frequent and severe metabolic instability
- Chronic kidney disease
- Severe cardiomyopathy with fibrotic changes

Solid Organ Transplantation: Issues

- Risk-benefit ratio and the role of transplant center proficiency
- Age of transplantation
  - Severity of PA
  - CKD
  - Cardiomyopathy
  - 18 yoa – a watershed moment
- Diet after transplant
- The natural course of PA after transplant
  - PA complications
  - Complications related to immunosuppression

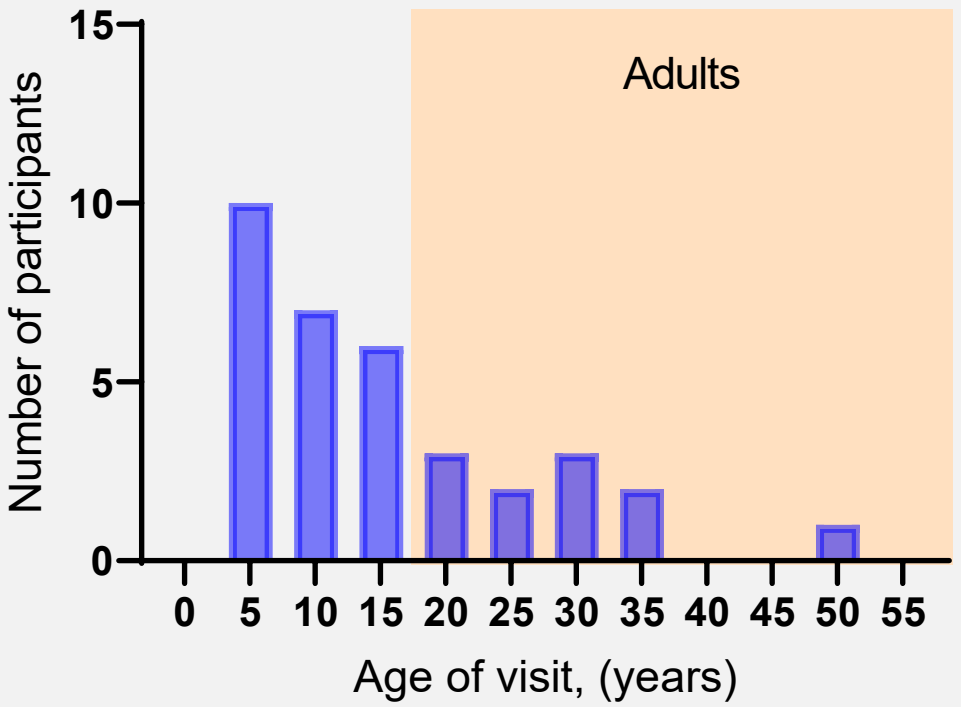
A Growing Adult Population Affected by OA

Age Distribution in the NIH mut type MMA



23% of MMA patients are > 18 yoa
(unpublished data)

Age Distribution in the NIH PA Cohort



45% of PA patients are > 18 yoa
(unpublished data)

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Emerging Therapies in PA

nature COMMUNICATIONS

ARTICLE

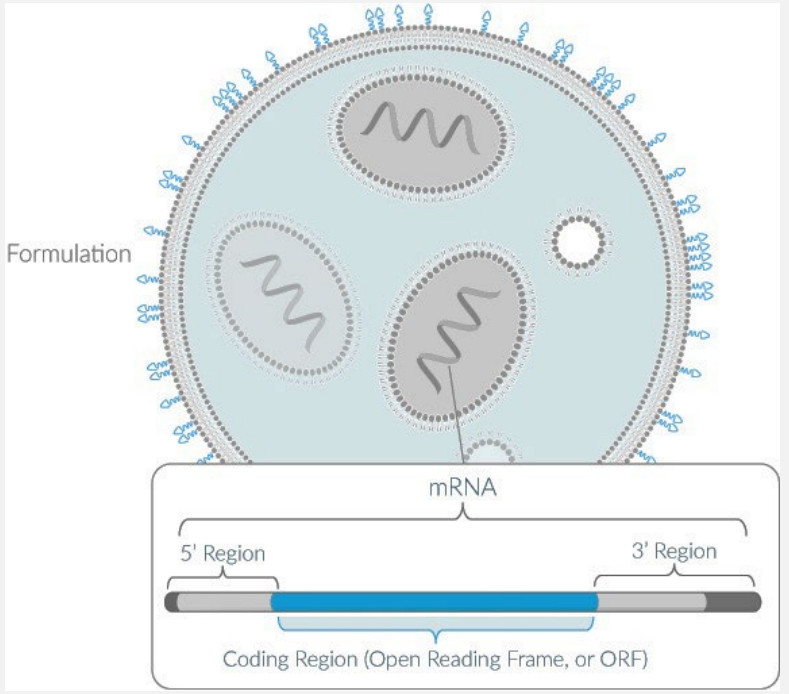
Check for updates

https://doi.org/10.1038/s41467-020-19156-3 OPEN

Dual mRNA therapy restores metabolic function in long-term studies in mice with propionic acidemia

Lei Jiang[1], Ji-Sun Park[1], Ling Yin[1], Rodrigo Laureano[1], Eric Jacquinet[1], Jinsong Yang[1], Shi Liang[1], Andrea Frassetto[1], Jenny Zhuo[1], Xinhua Yan[1], Xuling Zhu[1], Steven Fortucci[1], Kara Hoar[1], Cosmin Mihai[1], Christopher Tunkey[1], Vlad Presnyak[1], Kerry E. Benenato[1], Christine M. Lukacs[1], Paolo G. V. Martini[1]✉ & Lin T. Guey[1]✉

Jiang L, et al. Dual mRNA therapy restores metabolic function in long-term studies in mice with propionic acidemia. Nat Commun. 2020 Oct 21;11(1):5339. PMID: 33087718.



LNP contains both PCCA and PCCB mRNAs
IV injections (repeated): Lower metabolites in hypomorphic PA mice

ClinicalTrials.gov Identifier: NCT04159103

Recruitment Status : Not yet recruiting
First Posted : November 12, 2019
Last Update Posted : November 13, 2019

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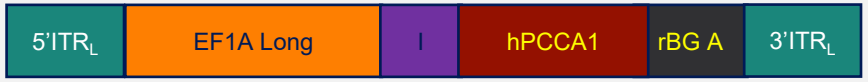
Systemic AAV9 gene therapy to treat neonatal lethal *Pcca* mice

AAV9-EF1L-hPCCA



EF1L

AAV9-EF1s-hPCCA-HPRE

EF1s-HPRE

Pcca lethal mice

LOW DOSE: 1E11 VG/pup
HIGH DOSE: 4E11 VG/pup
ROUTE: Retro-orbital injection (RO)

- **Survival (live or die)**
- **Phenotype (growth)**
- **Biomarker**
- **PCCA expression (Western)**
- **Transduction RNAscope**

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WITH NCATS: AAV GT for PCCA

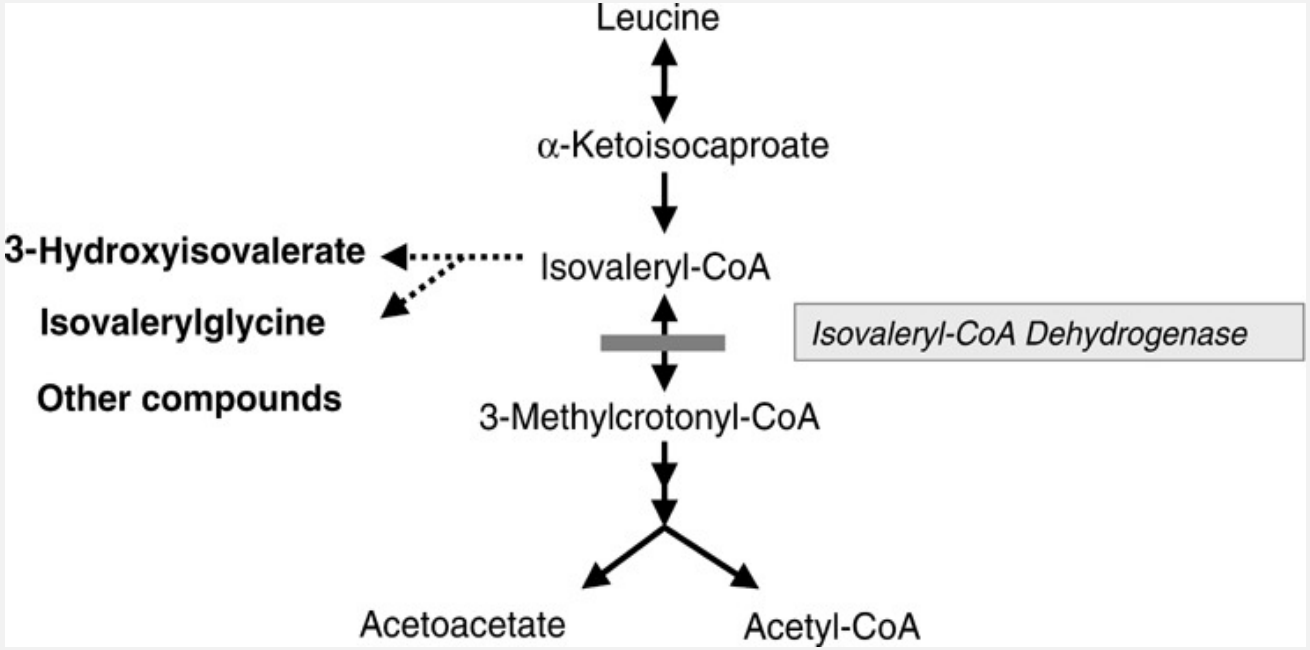
PaVe-GT: Paving the Way for Rare Disease Gene Therapies

The NCATS-led Platform Vector Gene Therapy (PaVe-GT) pilot project seeks to increase the efficiency of clinical trial startup by using the same gene delivery system and manufacturing methods for multiple rare disease gene therapies. We will make program results and regulatory documents publicly available, with the intention of benefiting future gene therapy clinical trials for very rare diseases.

https://pave-gt.ncats.nih.gov/

Isovaleric Acidemia

IVA



Vockley J, Ensenauer R. 2006. Isovaleric acidemia: New aspects of genetic and phenotypic heterogeneity. Am J Med Genet Part C Semin Med Genet 142C:95–103.

A characteristic smell of “dirty socks” may be present when the patient is acutely sick though, unlike other organic acidemias, the urine has no odor since the unconjugated isovaleric acid responsible for the odor is not excreted in urine in appreciable quantity. The odor may be best appreciated in body sweat or cerumen from the ear.

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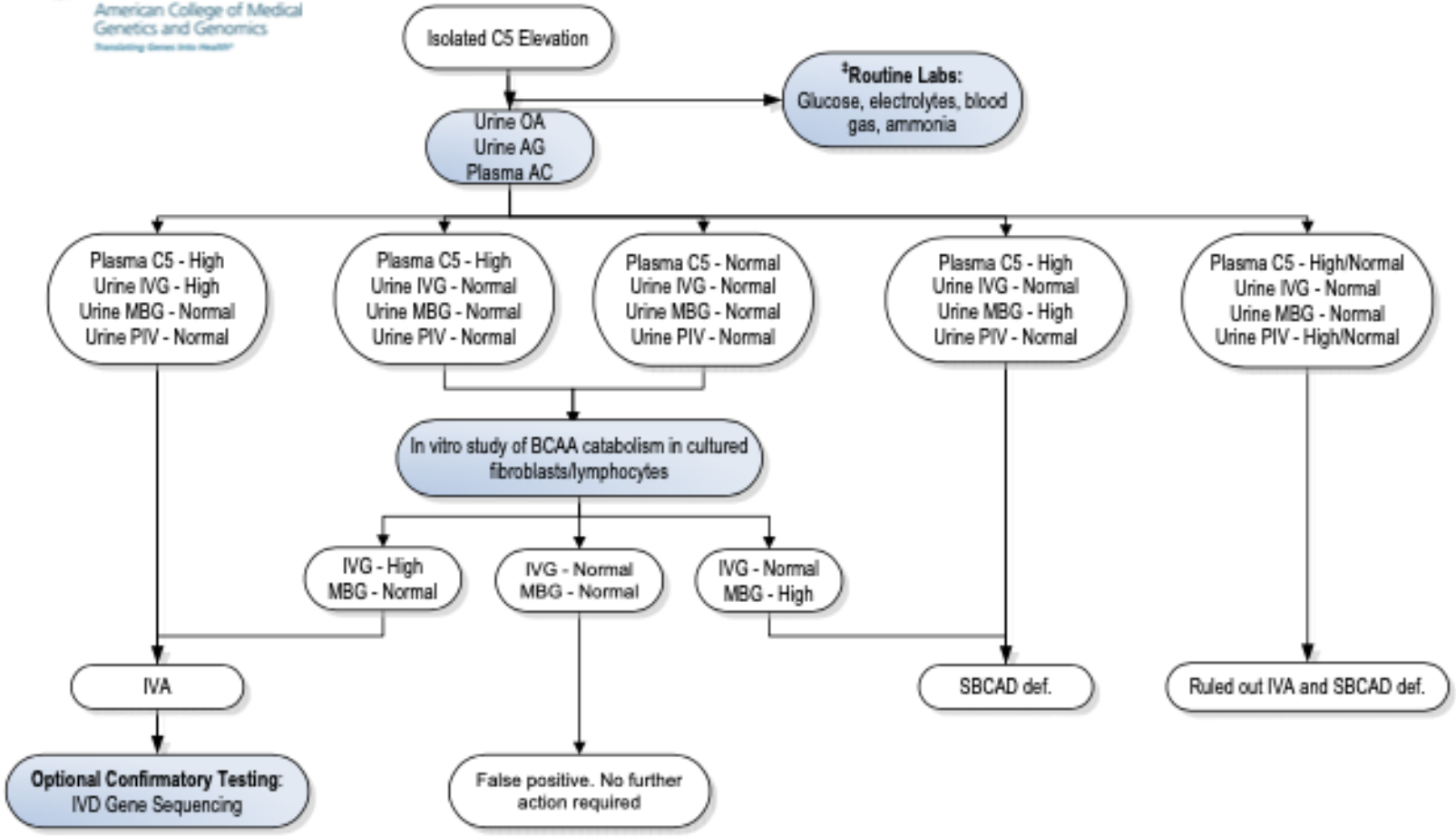
C5 Elevated (Isolated)



Abbreviations

AC = Acylcarnitine
AG = Acylglycine
IVA = Isovaleric acidemia
IVD = Isovaleryl-CoA dehydrogenase
IVG = Isovalerylglycine
MBG = 3-methylbutrylglycine
OA = Organic acid
PIV = Pivalic acid (antibiotic)
SBCAD = short/branched chain Acyl-CoA dehydrogenase

Key

‡ =When the positive predictive value of screening is sufficiently high and the risk to the infant is high, some initiate diagnostic studies that are locally available at the same time as confirmation of the screening result is done.

Actions are shown in shaded boxes; results are in the unshaded boxes.

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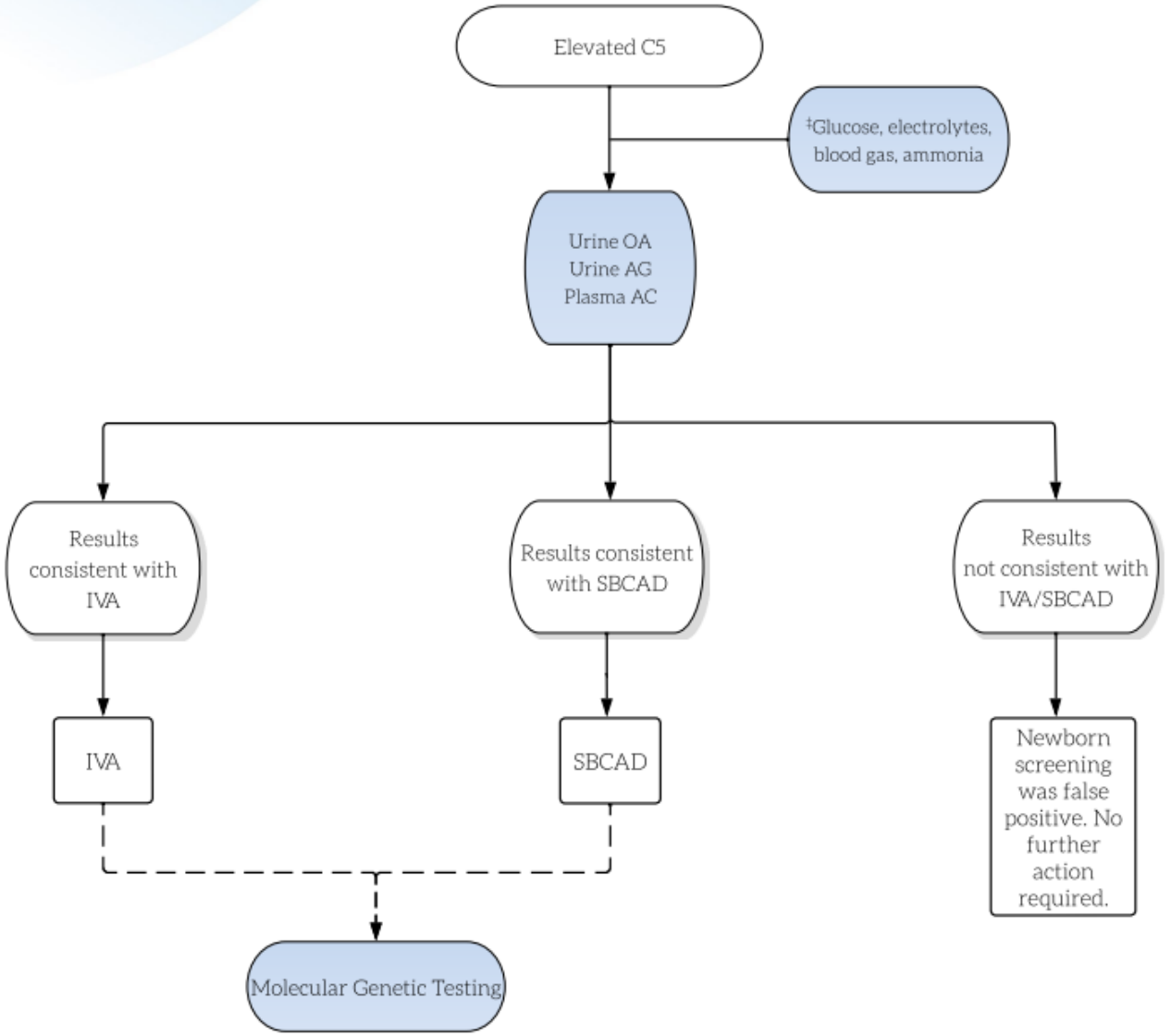
Isovaleric Acidemia: Increased C5 (isolated)



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Initial Diagnostic Evaluation for Suspected Isovaleric Acidemia

Evaluation following abnormal newborn screening with an elevated C5 acylcarnitine concentration	
Test	**Determination of**
Urine organic acid analysis	Multiple abnormal metabolites; isovalerylglycine concentration
Plasma acylcarnitine analysis	Isovalerylcarnitine concentration
Plasma carnitine analysis	Free carnitine concentration
Molecular genetic analysis	Common 932C>T (A282V) *IVD* gene mutation associated with a mild biochemical phenotype; otherwise heterogeneous mutations
Enzymatic analysis, optional (fibroblasts, lymphocytes)	Residual enzyme activity

Clinical Syndromes of IVA:

- Neonatal crisis +/- acidosis and hyperammonemia
  - Defines acute phenotype
- Infancy and Childhood
  - Can have misc symptoms, delay, hypotonia, vomiting, food aversions, DKA-like episodes
  - PANCREATITIS
- Adult
  - Crisis under duress

Therapy	Biochemical phenotype	
	Metabolically mild or intermediate	**Metabolically severe**
Prevention of metabolic crisis	Close clinical observation; promote anabolism during illness	
Diet	None	Protein restriction
Medication	Carnitine (30–50 mg/kg per day) if plasma free carnitine concentration is low	Carnitine (100 mg/kg per day)
	None	Glycine (150–250 mg/kg per day)

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Molecular Genetics and Metabolism Reports 12 (2017) 16–22

Contents lists available at ScienceDirect

Molecular Genetics and Metabolism Reports

journal homepage: www.elsevier.com/locate/ymgmr

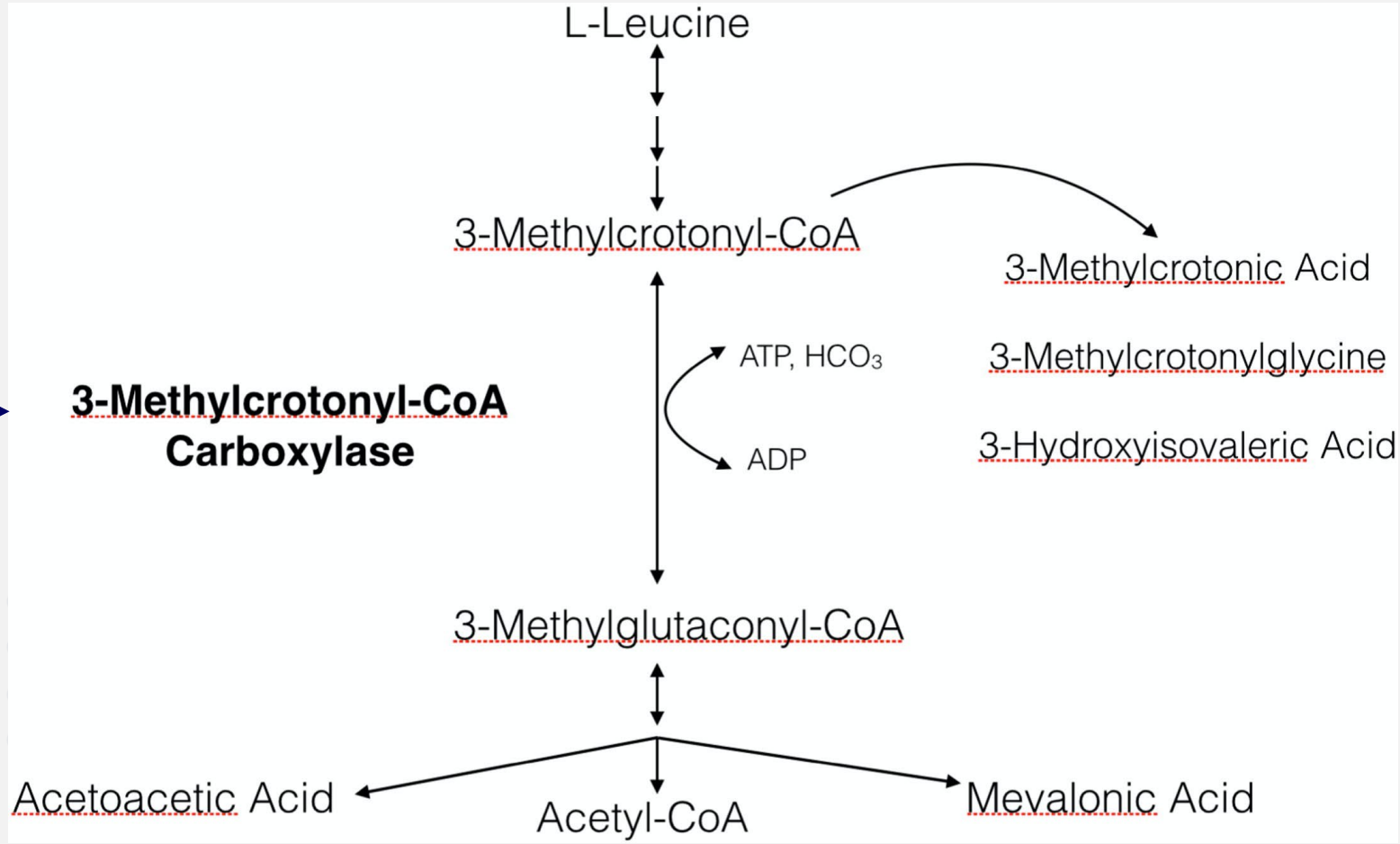
Dietary practices in isovaleric acidemia: A European survey

Results: Information on 140 patients with IVA from 39 centres was reported. 133 patients (38 centres) were given a protein restricted diet. Leucine-free amino acid supplements (LFAA) were routinely used to supplement protein intake in 58% of centres. The median total protein intake prescribed achieved the WHO/FAO/UNU [2007] safe levels of protein intake in all age groups. Centres that prescribed LFAA had lower natural protein intakes in most age groups except 1 to 10 y. In contrast, when centres were not using LFAA, the median natural protein intake met WHO/FAO/UNU [2007] safe levels of protein intake in all age groups. Enteral tube feeding was rarely prescribed.

Conclusions: This survey demonstrates wide differences in dietary practice in the management of IVA across European centres. It provides unique dietary data collectively representing European practices in IVA which can be used as a foundation to compare dietary management changes as a consequence of the first E-IMD IVA guidelines availability.

3-MCC Deficiency

3-methylcrotonyl-CoA carboxylase deficiency (3-MCC)



Biotin cycle ↔ **3-Methylcrotonyl-CoA Carboxylase**

3-Hydroxyisovaleric Acid ↔ **C5-OH**

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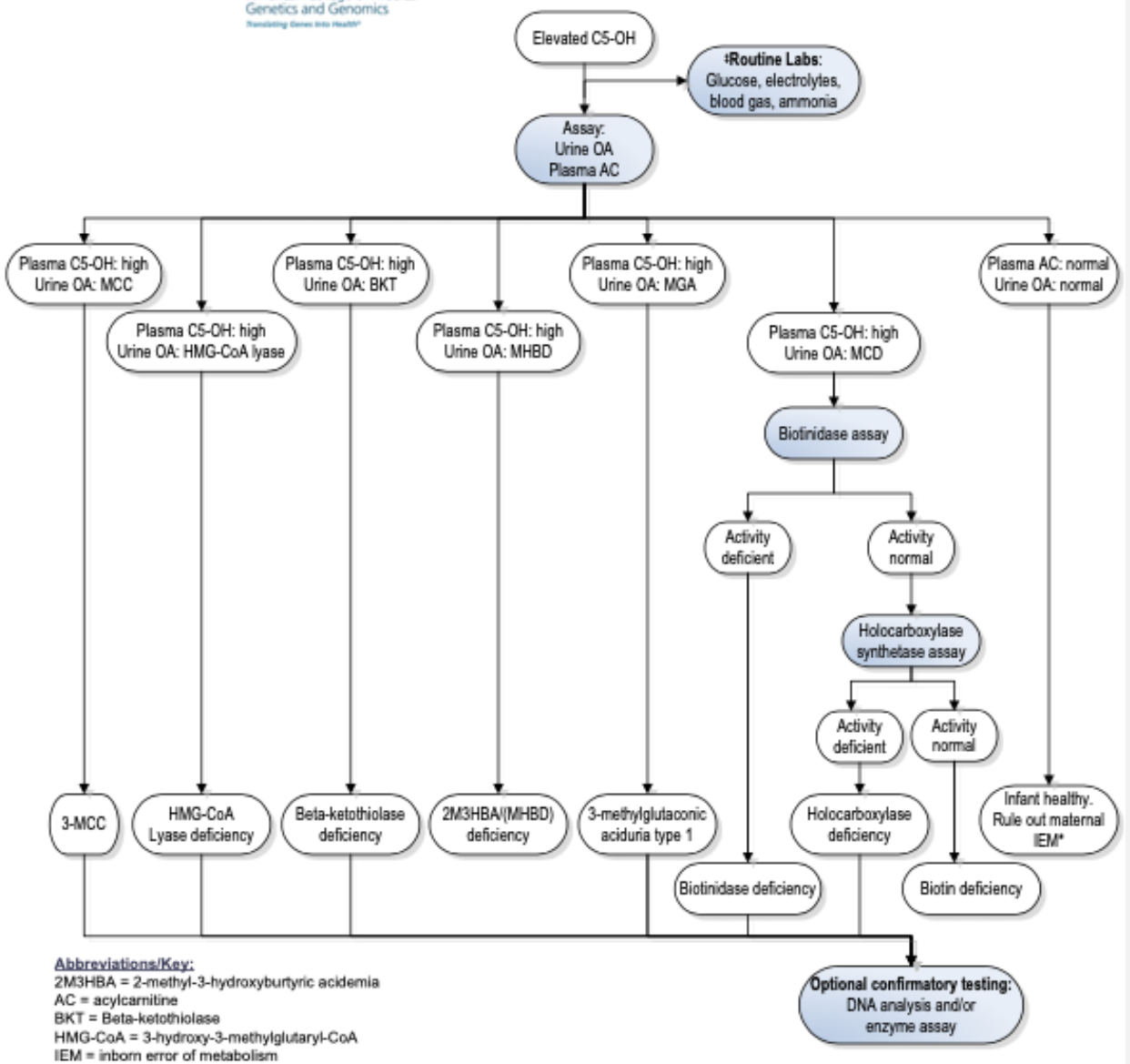
C5-OH Elevated



Abbreviations/Key:
2M3HBA = 2-methyl-3-hydroxyburtyric acidemia
AC = acylcarnitine
BKT = Beta-ketothiolase
HMG-CoA = 3-hydroxy-3-methylglutaryl-CoA
IEM = inborn error of metabolism
MCC = methylcrotonyl-CoA carboxylase
MCD = multiple carboxylase deficiency
MGA = 3-methylglutaconic aciduria
MHBD = 2-methyl-3-hydroxybutyryl-CoA dehrodrogenase
OA = organic acid

* = Maternal MCC and holocarboxylase deficiency have been reported as having been identified in newborn screening.
‡ = When the positive predictive value of screening is sufficiently high and the risk to the newborn is high, some initiate diagnostic studies that are locally available at the same time as confirmation of the screening result is done.

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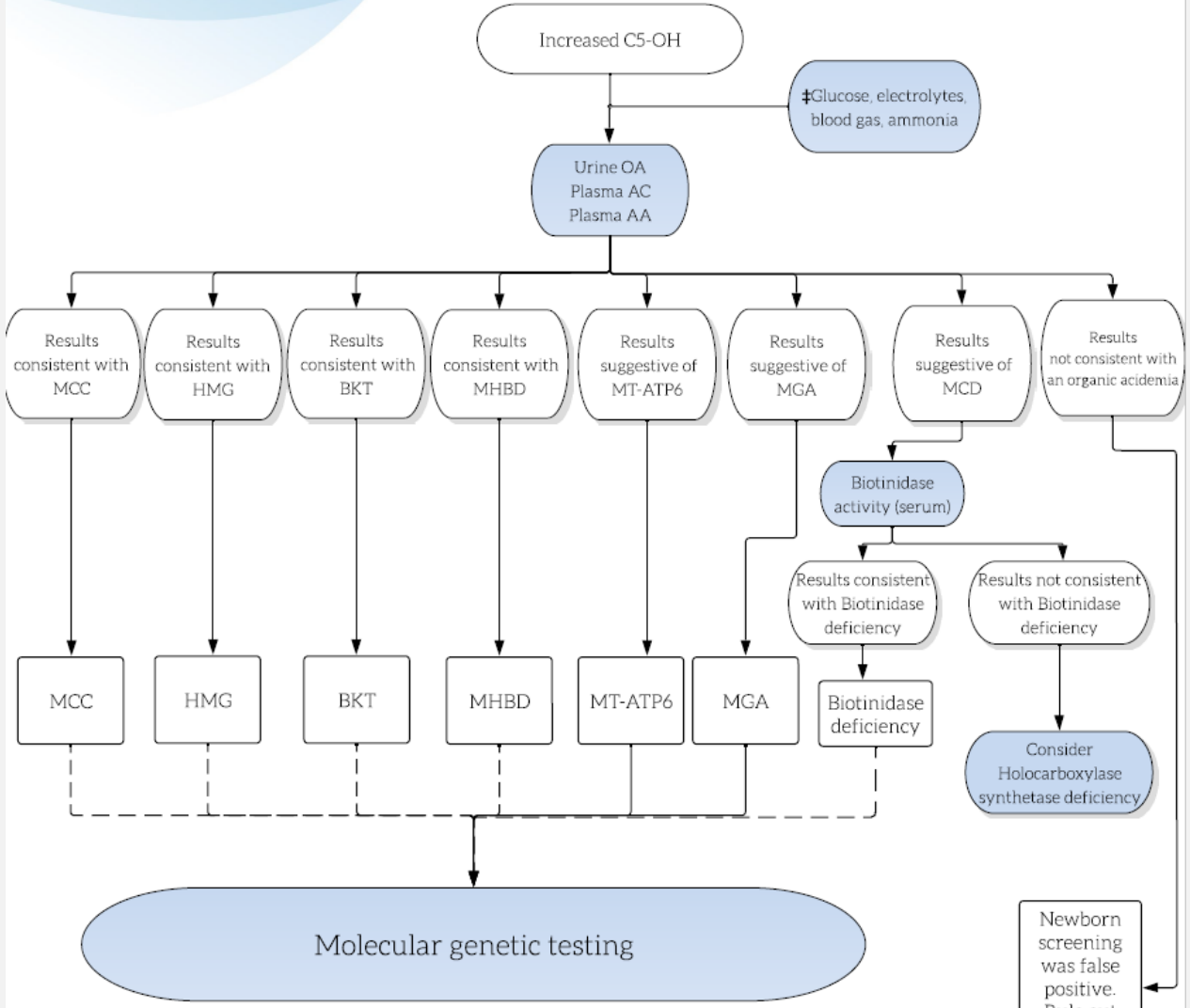
Organic Acidemias: Elevated C5-OH



Key

- Actions are shown in shaded ovals; results are in the unshaded ovals. Diagnostic outcomes are shown in boxes.
- Dashed line reflects an optional test.
- †May be performed locally as a rapid screen to assess severity.

Abbreviations

2M3HBA = 2-Methyl-3-hydroxybutyric acidemia
AA = amino acids
AC = acylcarnitines
BKT = Beta-ketothiolase deficiency
HMG = 3-Hydroxy-3-methylglutaryl-CoA lyase deficiency
IEM = inborn error of metabolism
MCC = 3-Methylcrotonyl-CoA carboxylase deficiency
MCD = Multiple carboxylase deficiency
MGA = 3-Methylglutaconic aciduria
MHBD = 2-Methyl-3-hydroxybutyryl-CoA dehydrogenase deficiency

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3-methylcrotonyl-CoA carboxylase deficiency (3-MCC)

- Caused by mutations in MCCC1 or MCCC2 encoding the α and β subunit of MCC, respectively
- Detected by expanded NS with increased C5-OH
- One of the most common IEMs diagnosed by NBS with a prevalence ranging from 1:2400 to 1:68,000
- Characteristic urine metabolites: 3-OH isovaleric acid and 3-methylcrotonylglycine
- Characteristic plasma metabolites: 3-hydroxyisovalerylcarnitine (C5OH), some with secondary carnitine deficiency
- The phenotype is highly variable ranging from acute neonatal onset with fatal outcome to asymptomatic adults
    - Not rare: mother affected and infant + C5-OH and/or low C0

3-methylcrotonyl-CoA carboxylase deficiency (3-MCCD)

Grünert et al. Orphanet Journal of Rare Diseases 2012, 7:31
http://www.ojrd.com/content/7/1/31

ORPHANET JOURNAL OF RARE DISEASES

RESEARCH Open Access

3-methylcrotonyl-CoA carboxylase deficiency: Clinical, biochemical, enzymatic and molecular studies in 88 individuals

Sarah C Grünert[1,2], Martin Stucki[1,3], Raphael J Morscher[1], Terttu Suormala[1,4], Celine Bürer[1], Patricie Burda[1], Ernst Christensen[5], Can Ficicioglu[6], Jürgen Herwig[7], Stefan Kölker[8], Dorothea Möslinger[9], Elisabetta Pasquini[10], René Santer[11], K Otfried Schwab[2], Bridget Wilcken[12], Brian Fowler[1,4], Wyatt W Yue[13] and Matthias R Baumgartner[1,3*]

Molecular Genetics and Metabolism 106 (2012) 439–441

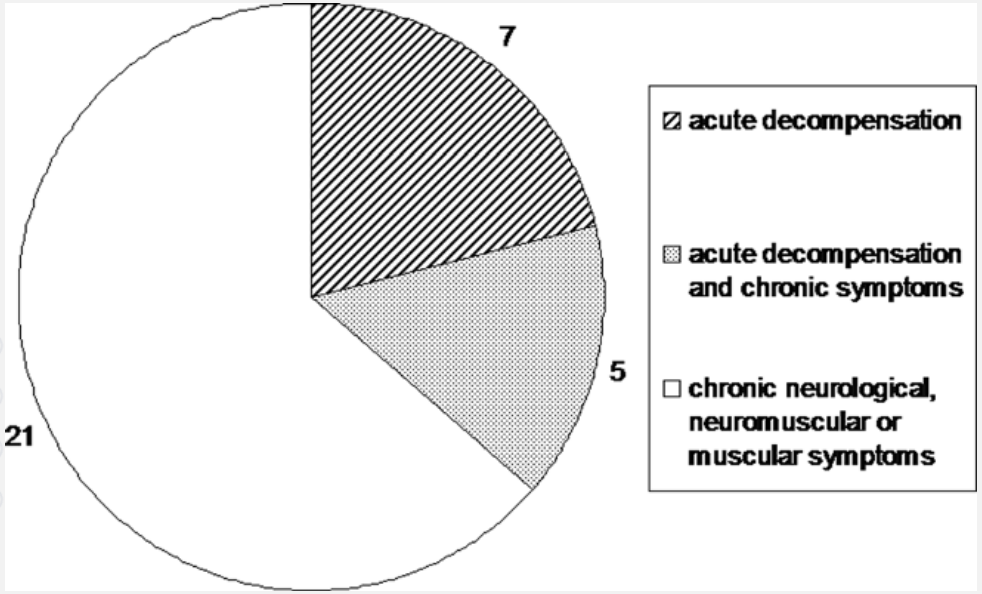
Contents lists available at SciVerse ScienceDirect

Molecular Genetics and Metabolism

journal homepage: www.elsevier.com/locate/ymgme

Outcome of infants diagnosed with 3-methyl-crotonyl-CoA-carboxylase deficiency by newborn screening

Georgianne L. Arnold [a,*], Denise Salazar [b], Julie A. Neidich [c], Pim Suwannarat [d], Brett H. Graham [e], Uta Lichter-Konecki [f], Annet M. Bosch [g], Kristina Cusmano-Ozog [f], Greg Enns [h], Erica L. Wright [i], Brendan C. Lanpher [f], Natalie N. Owen [j], Mark H. Lipson [k], Roberto Cerone [l], Paul Levy [m], Lee-Jun C. Wong [e], Antal Dezsofi [n]



"Although residual enzyme activity was clearly related to metabolite elevation, there was no apparent relationship with other measures of outcome. The number of reports of neurologic abnormalities or metabolic symptoms (poor feeding, hypoglycemia, fasting intolerance, etc.) is concerning, but the significance is unclear in this retrospective sample. "

Analysis of cases of 3-methylcrotonyl CoA carboxylase deficiency (3-MCCD) in the California newborn screening program reported in the state database

Christina Lam [a,*,1], Jennifer M. Carter [b], Stephen D. Cederbaum [a,c,d], Julie Neidich [e], Natalie M. Gallant [a], Fred Lorey [f], Lisa Feuchtbaum [f], Derek A. Wong [a]

[a] Department of Pediatrics, University of California, Los Angeles, CA, USA
[b] Public Health Foundation Enterprises, City of Industry, CA, USA
[c] Department of Psychiatry, University of California, Los Angeles, CA, USA
[d] Department of Human Genetics, University of California, Los Angeles, CA, USA
[e] Ambry Genetics, Aliso Viejo, CA, USA
[f] California Department of Public Health, Genetic Disease Screening Program, Richmond, CA, USA

- 2,959,108 infants screened .. ….71 infants diagnosed with 3-MCCD for an overall incidence of 1:41,676.
- 49% received dietary modification and 44% received carnitine.
- 15% of cases : lethargy, vomiting, irritability, ketosis, poor feeding, or poor tone.
- The majority were completely normal.
- ? significant numbers of individuals receiving treatment for 3-MCCD may not have a clinically significant condition.

Multiple Carboxylase Deficiency

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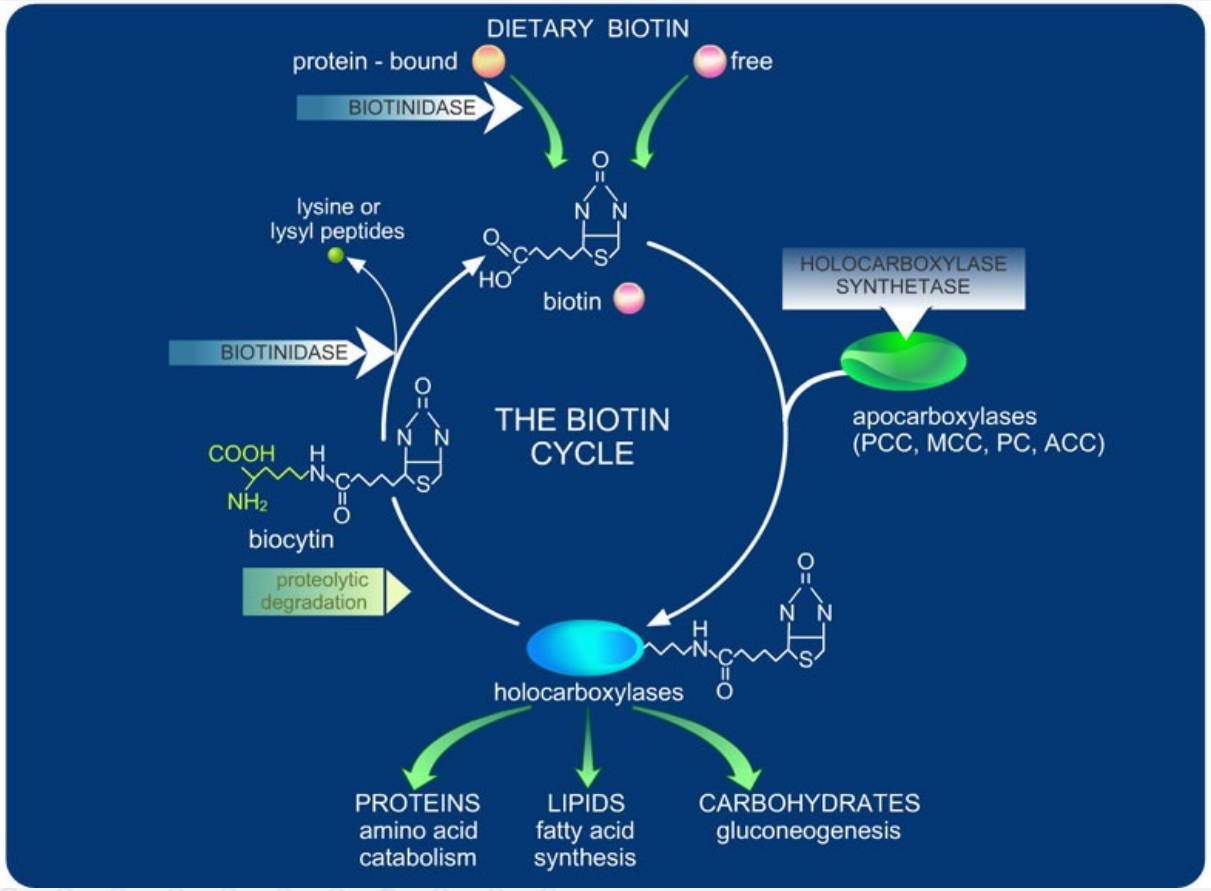
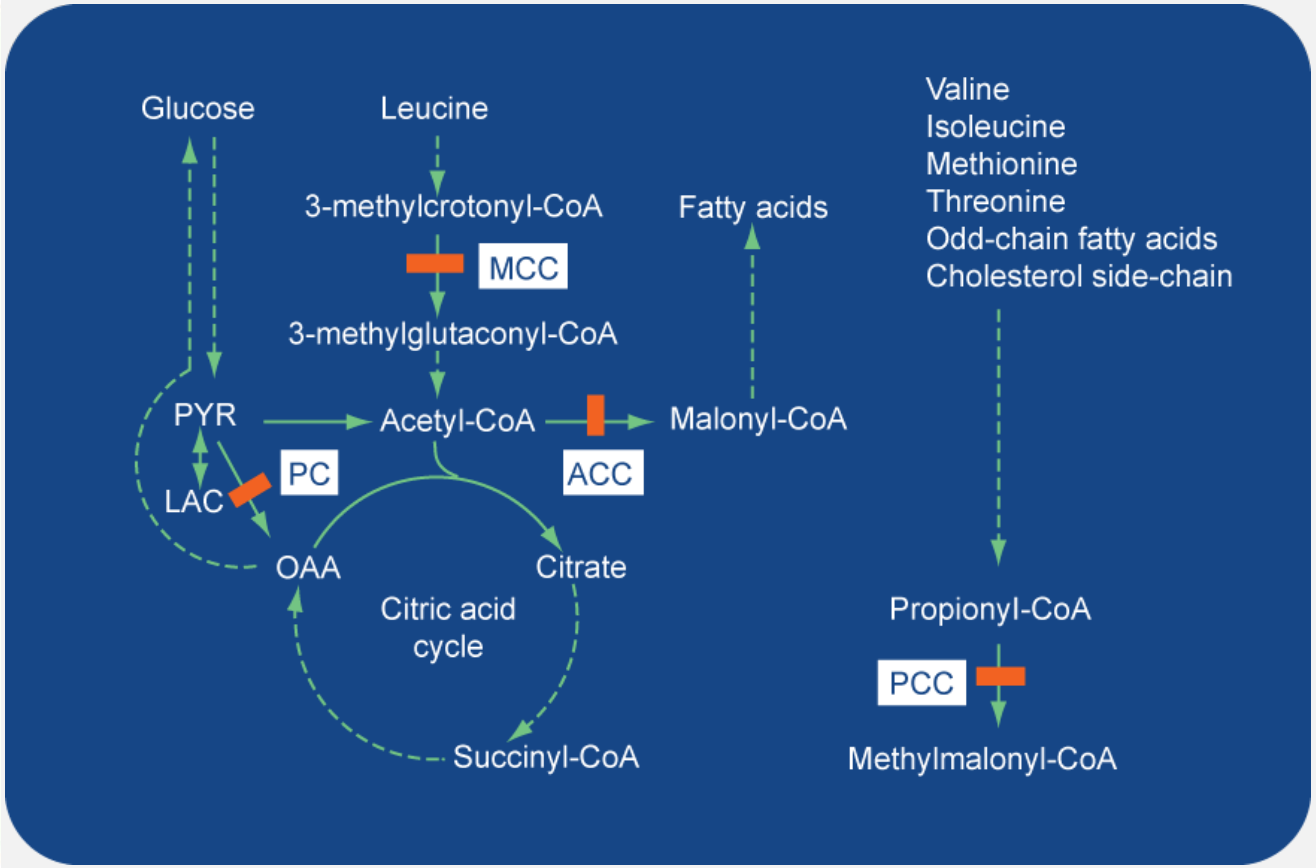
Biotin cycle……



….. Biotinylated enzymes



Inborn Metabolic Diseases, 4th edition (Fernandez, Saudubray et al)

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Inborn errors of biotin transport, recycling, and metabolism

- Biotinidase deficiency (1/60,000)
  - Detected in the NS blood spot
- Holocarboxylase synthetase (HCS) deficiency
  - Both cause multiple carboxylase deficiency
  - 3 methylcrotonyl-CoA carboxylase
  - Pyruvate carboxylase
  - Propionyl-CoA carboxylase
  - Acetyl-CoA carboxylase
- Biotin-thiamine-responsive basal ganglia disease (BTBGD) (*SLC19A3)* specific cerebral transporter defect)

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GENETEST REVIEW | Genetics inMedicine
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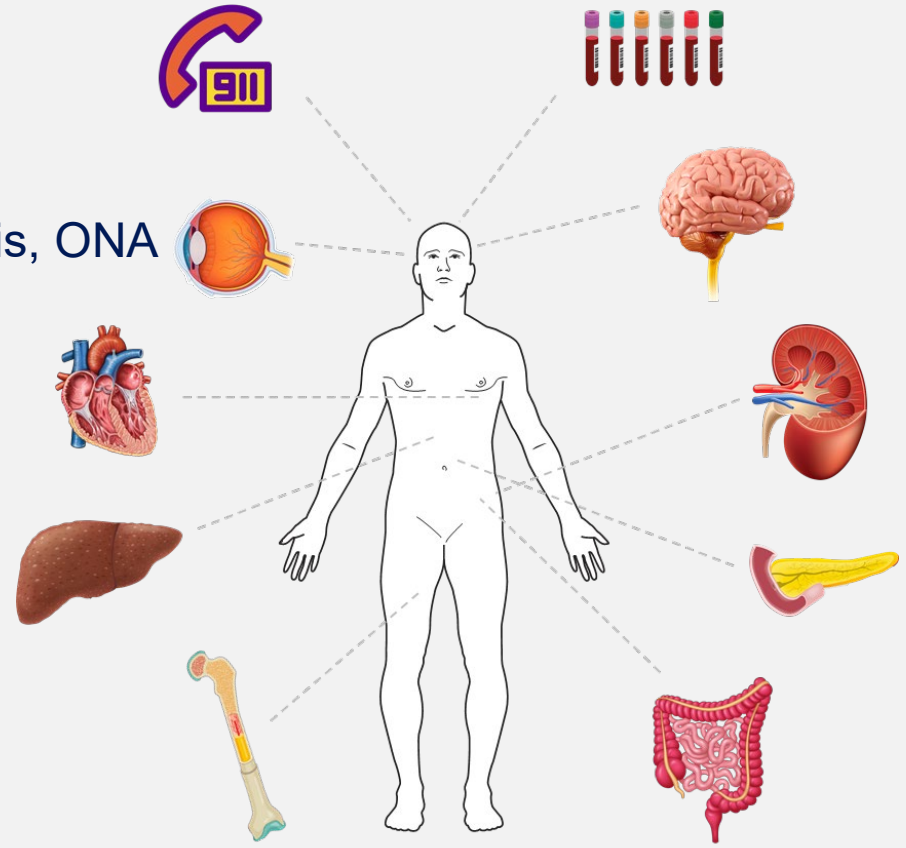
Biotinidase deficiency: "if you have to have an inherited metabolic disease, this is the one to have"

Barry Wolf, MD, PhD[1,2]

BIOTINIDASE DEFICIENCY

eczematous skin rash; alopecia



hypotonia; seizures; ataxia;developmental delay; **hearing loss**; progressive spastic paresis and myelopathy

conjunctivitis, ONA

hyperventilation, laryngeal stridor, and apnea

ketolactic acidosis, organic aciduria, and hyperammonemia

Recurrent viral or fungal infections
Candidiasis

Biotinidase deficiency

- Confirmation: biotinidase enzyme activity in serum/plasma.
- Mutation analysis (genotyping) pending ambiguity of diagnosis by enzymatic activity.
- Consider: audiological evaluation for sensorineural hearing loss, ophthalmological evaluation for optic atrophy and other eye abnormalities
- Follow up of patients ascertained through NBS and adequately treated

- 142 children with biotinidase deficiency identified by newborn screening in Michigan over a 25-year period and followed in our clinic; 22 had profound deficiency and 120 had partial deficiency.

- Individuals with biotinidase deficiency ascertained by newborn screening and treated since birth appeared to exhibit normal physical and cognitive development. If an individual does develop symptoms, after compliance and dosage issues are excluded, then other causes must be considered.

Genet Med **17** 3, 205–209.

Neonatal screening for biotinidase deficiency: A 30-year single center experience

Francesco Porta*[,1], Veronica Pagliardini[1], Isabella Celestino, Enza Pavanello, Severo Pagliardini, Ornella Guardamagna, Alberto Ponzone, Marco Spada

Department of Pediatrics, University of Torino, Italy

- 1,097,894 newborns screened, 461 were recalled, and 18 were identified as affected by complete or partial biotinidase deficiency (incidence 1:61,000, false positive rate 0.04%).
-
- The common missense mutation p.Q456H was found in 80% of patients with profound biotinidase deficiency.
- All detected patients were treated with Biotin therapy (10–20 mg/day)
- Afforded the full prevention of clinical symptoms in all patients with no adverse effects.
- These excellent outcomes confirm that newborn screening for biotinidase deficiency is a very effective secondary prevention program.

Holocarboxylase synthase deficiency (HCS)

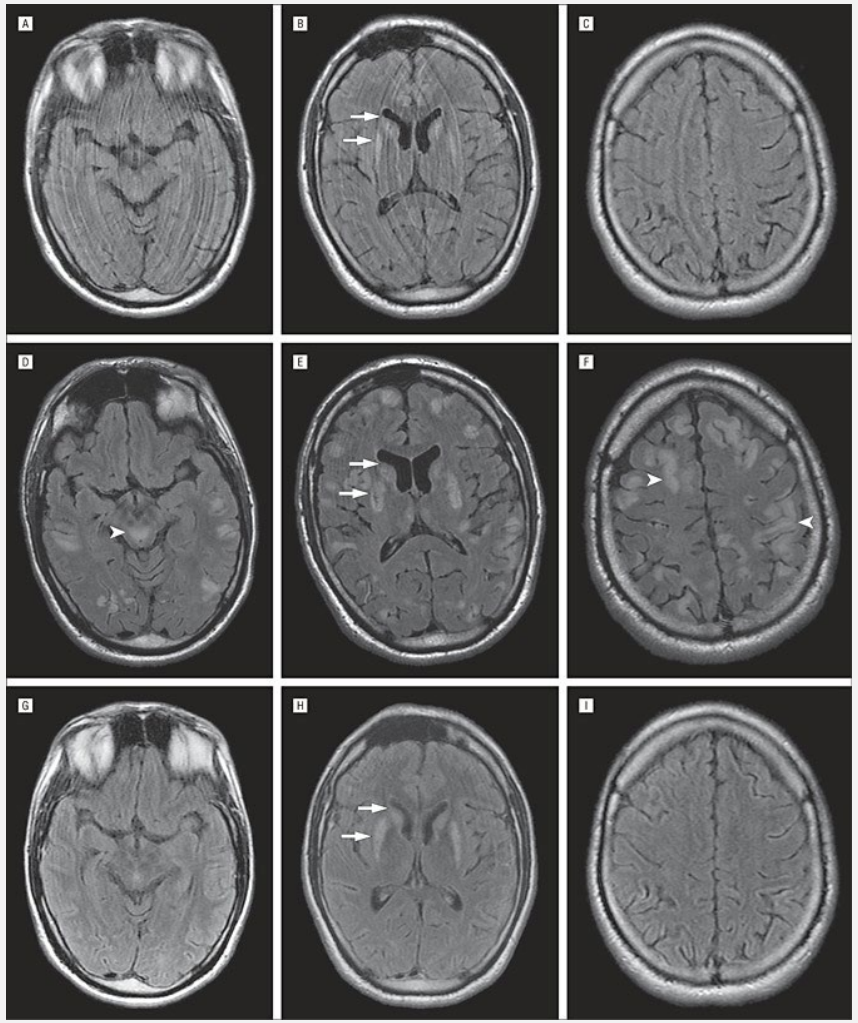
- Earlier and more severe than biotinidase deficiency
- Detected via of elevated C5-OH
- Urine organic acid profile may demonstrate elevated lactic, 3-OH isovaleric, 3-OH propionic, 3-MCC, 2-methylcitric, and tiglylglycine consistent with loss of function of the carboxylases.
- Confirmation: molecular genetics (*HLCS*)
- Acute presentation of sick neonate:
    - Lethargy and hypothermia
    - Vomiting
    - Tachypnea and apnea
    - Metabolic acidosis, elevated lactate
    - Alopecia and rash

Chronic holocarboxylase synthase deficiency

- Progressive encephalopathy
- Seizures
- Hypotonia
- Developmental delay
- Ataxia
- Extrapyramidal signs
- Alopecia and rash
- Recurrent acidosis

Biotin responsive basal ganglia disease

- Age of onset 1–14 years
- Presentation
  - Subacute encephalopathy
  - Progress to cogwheel rigidity with dystonia and quadriparesis
- Symptoms improve with biotin (5–10 mg/kg/day) or biotin + thiamine
  - Early treatment with no neurologic sequelae
  - Symptoms return in month if stopped
- Mutations in *SLC19A3* gene (thiamine transporter)



Debs, *et al.*, 2010 Arch Neurol. **67:** 126-30

Treatment of biotin disorders

- Biotin
  - HCS 10 or 20 up to 100 mg/day
  - Biotinidase deficiency 5-10 mg/day
  - BTBGD Biotin (5-10 mg/kg/day) and thiamine (up to 40 mg/kg/day with a maximum of 1500 mg daily)
- Restriction of protein intake not necessary
- Acutely ill patients need urgent metabolic protocol
- Prognosis is excellent with early institution of biotin
- If therapy is discontinued, symptoms recur within several weeks to months depending on disease severity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OARS Fall 2019

Acknowledgments

Organic Acid Research Section (present)

Randy Chandler MB, PhD
Eu Young Choi, PhD
Susan Ferry BS, RN
PamelaSara Head, PhD
Sungkook Hong, PhD
Christopher Jordan, MD
Stefanos Katsoukous, BS
Lina Li MD, PhD
Irini Manoli MD, PhD
Francis May, MD candidate
Samantha McCoy, BS
Sam Myung, BS
Darwin Romero, BS
Oleg Shchelochkov, MD
Stephanie Smith BS, MBA
Jennifer Sloan PhD, MSGC
Carol Van Ryzin BS, RN, PNP
Leah Venturoni, PhD

Organic Acid Research Section (past 5 years)

Nate Achilly MD, PhD candidate
Madeline Arnold, PhD candidate
Katherine Ellis, MD, PhD candidate
Maddie Epping, MD, PhD candidate
Jamie Fraser MD, PhD Assistant Prof
Jack Gagne, MD candidate
Elizabeth Harrington, GC
Emily Iisko, PhD candidate
Brandon Hubbard MD, PhD candidate
Alexander Lesser, MD, PhD candidate
Joel Pardo, MD, PhD candidate
Jess Schneller, PhD Novadiskus
Julien Senac PhD Medical Device Consulting
Justin Sysol MD, PhD ICU fellow
Donna Raval MD MFM

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